benzamide (19.4 g, 0.1 mole) and 1,2-dibromobutane (21.6 g, 0.01 mole) in ethoxyethanol was refluxed for 1 hr. NaOAc (8.2 g, 0.01 mole) was added and the refluxing was continued for 1 hr. Ether (50 ml) and H_2O (200 ml) were added and the unreacted thioamide was filtered. The aqueous extract was treated with $NaClO_4$ (5.0 g) to give the product as the perchlorate salt, mp 149–151°, yield 7.0 g (28% based on unrecovered thioamide), λ_{max} 386 mμ. *Anal.* ($C_{14}H_{21}ClN_2O_4S$) C, H, Cl, N, S.

2-(*p*-Dimethylaminophenyl)-3-methyl-4H-5,6-dihydro-1,3-thiazinium Iodide (21).—The thioamide was treated with 1,3-dibromopropane and NaOAc in ethoxyethanol as described above. KI was added to the aqueous solution of the bromide salt to give the iodide, mp 213–214.5° (from EtOH) in 26% yield, λ_{max} 373 mμ. *Anal.* ($C_{13}H_{19}IN_2S$) C, H, I, N, S.

S-Methyl-N-methyl-*p*-dimethylaminothiolbenzimidate (24).—A solution of **4** (1.9 g, 0.01 mole) and MeI (1.42 g, 0.01 mole) in MeOH (10 ml) was refluxed for 1 hr. The solution was evaporated, and the residue was extracted (H_2O). Addition of $NaHCO_3$ to the aqueous extract gave **24**, mp 76–77°, yield 0.7 g (34%), λ_{max} 295 mμ. *Anal.* ($C_{11}H_{16}N_2S$) C, H, N, S.

***p*-Dimethylamino-N,N-dimethylthiobenzamide (22).**—A solution of *p*-dimethylamino-N,N-dimethylbenzamide[4] (17.5 g, 0.09 mole) and P_2S_5 (5.6 g, 0.025 mole) in 100 ml pyridine was refluxed for 40 min. The product was isolated by diluting the reaction mixture with ice–water and recrystallizing the precipitate from MeOH, mp 103–104°, yield 11.5 g (61%), λ_{max} 335, 236 mμ. *Anal.* ($C_{11}H_{16}N_2S$) C, H, N, S.

S-Methyl-N,N-dimethyl-*p*-dimethylaminothiolbenzimidate Iodide (23).—A suspension of *p*-dimethylamino-N,N-dimethylthiobenzamide (2.1 g, 0.01 mole) in Et_2O (20 ml) was treated with excess MeI (3 ml). The solution became clear, and the product then separated out rapidly as an oil which crystallized on standing, yield 3.4 g (97%), mp 120° dec, λ_{max} 386, 265 mμ. *Anal.* ($C_{12}H_{19}IN_2S$) C, H, I, N, S.

Diquaternary salt (25). (a) The thiolbenzimidate (**24**) (0.45 g, 2.2 mmoles) was dissolved in excess MeI (3 ml) and the solution was allowed to stand overnight. Evaporation of the solution gave a quantitative yield of **25**, mp 210° (vigorous decomposition), λ_{max} 265 mμ.

(b) The monoquaternary salt (**23**) (0.35 g) was refluxed with MeI (5 ml) in MeOH (5 ml) for 15 min. Evaporation of the solution gave the same product (0.45 g), mp 210° dec. *Anal.* ($C_{13}H_{22}I_2N_2S$) C, H, I; N: calcd, 5.69; found, 6.27.

A sample of the diquaternary salt was dissolved in H_2O at room temperature. The solution was filtered after 1 hr, and the filtrate was concentrated under reduced pressure, giving S-methyl *p*-dimethylaminothiolbenzoate methiodide (**26**), mp 174–176° (from MeOH–Et_2O). *Anal.* ($C_{11}H_{16}INOS$) C, H, I, N, S.

2-(*p*-Anisyl)-3,4-dimethylthiazolium Iodide (27a).—2-(*p*-Anisyl)-4-methylthiazole,[5] mp 55–57°, was heated with excess MeI in a pressure bottle at 100° for 1 hr. The solid residue was crystallized from MeOH–Et_2O to a melting point of 190–192°, yield 51%, λ_{max} 306 mμ. *Anal.* ($C_{12}H_{14}INOS$) C, H, I, N, O, S.

2-(*p*-Anisyl)-3-ethyl-4-methylthiazolium Iodide (27b).—The thiazole described above was heated with EtI in a pressure bottle at 100° for 6 hr, giving the product, mp 194–196° (from EtOH), in 49% yield, λ_{max} 306 mμ. *Anal.* ($C_{13}H_{16}INOS$) C, H, I, N, O, S.

Acknowledgment.—The authors are indebted to Dr. A. O. Geiszler for invaluable help in the coordination of the research program.

(8) C. M. Suter and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 1585 (1930).

3,4-Dihydro-2(1H)-quinazolinones

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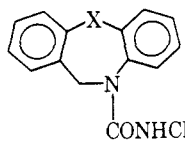
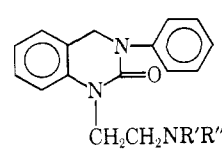
A series of 1- and 3-aminoalkyl-3,4-dihydro-2(1H)-quinazolinones was synthesized and the antiinflammatory activity investigated. Several of the compounds were equal to or better than phenylbutazone in one of the animal models of inflammation.

We have observed consistent but rather weak antiinflammatory activity among many simple dialkylaminoalkylureas. Attempts to increase this activity have involved the preparation of various cyclic derivatives of these compounds. Our first approach involved the synthesis of ureas derived from tricyclic amines of the type I.[1] These derivatives were also



I

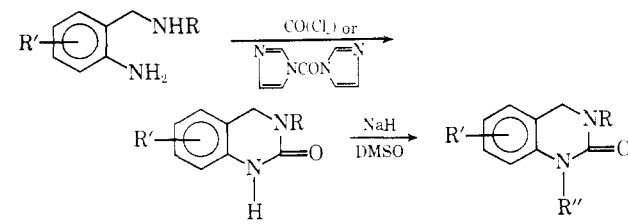


II

active as antiinflammatory agents but the potencies did not approach an acceptable level. Another type of cyclic derivative II, the 3-phenyl-1-dialkylaminoalkyl-3,4-dihydro-2(1H)-quinazolinones, was investigated and the lead compounds exhibited more potent antiinflammatory activity. A large number of compounds were then synthesized including the isomeric 3-dialkylaminoalkyl-3,4-dihydro-2(1H)-quinazolinones, and their antiinflammatory activity was investigated. A stimulus to this work was the fact that 3-phenyl-3,4-dihydro-2(1H)-quinazolinone was the only compound of this type previously reported in the literature.[2]

The 3-substituted 3,4-dihydro-2(1H)-quinazolinones were synthesized *via* ring closure of the appropriate diamine either with phosgene (method E) or with 1,1′-carbonyldiimidazole (method F) as shown in Chart I.

CHART I

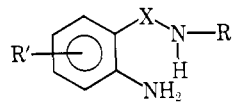


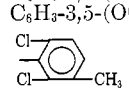
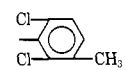
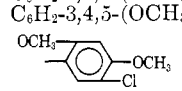
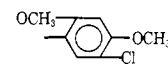
The ring closure with phosgene was carried out by the addition of a solution of phosgene in toluene to a solution of the diamine followed by reflux. The yields in this reaction were usually low and the products difficult to purify. In contrast, refluxing an equimolar quantity of the diamine with 1,1′-carbonyldiimidazole in THF gave an excellent yield of the quinazolinone, in many cases analytically pure. Alkylations of the

(1) W. E. Coyne and J. W. Cusic, *J. Med. Chem.*, **10**, 541 (1967).

(2) M. Busch, *Ber.*, **25**, 2853 (1892).

Table I



Compd	X	R	R′	Mp, °C	Solvent	Method	Formula[c]
1	CO	C_6H_5	H	117–119	EtOH	A	$C_{13}H_{12}N_2O$
2	CH_2	C_6H_5	H	81–83	EtOH		$C_{13}H_{14}N_2$
3	CO	C_6H_4Cl-*p*	H	136–142	EtOH	A	$C_{13}H_{11}ClN_2O$
4	CH_2	C_6H_4Cl-*p*	H	85–91	EtOH–H_2O		$C_{13}H_{13}ClN_2$
5	CO	C_6H_5	4-Cl	146–151	EtOH	A	$C_{13}H_{11}ClN_2O$
6	CH_2	C_6H_5	4-Cl	84–86	EtOH–H_2O		$C_{13}H_{13}ClN_2$
7	CO	C_6H_3-2,4-$(CH_3)_2$	H	125–130	EtOH	A	$C_{15}H_{16}N_2O$
8	CH_2	C_6H_3-2,4-$(CH_3)_2$	H	65–75	EtOH–H_2O		$C_{15}H_{18}N_2$
9	CO		H	141–147	EtOH	A	$C_{17}H_{22}N_2O$
10	CH_2		H	97–99	EtOH		$C_{17}H_{24}N_2$
11	CO	$CH_2C_6H_5$	H	117–122		B	$C_{14}H_{14}N_2O$
12	CH_2	$CH_2C_6H_5$	H	Oil			$C_{14}H_{16}N_2$
13	CO	CH_2—CH=CH_2	H	85–92	EtOH–H_2O	B	$C_{10}H_{12}N_2O$
14	CH_2	$CH_2CH_2CH_3$	H	Oil			
15	CO	C_6H_2-3,4,5-$(OCH_3)_3$	H	214–218	THF	A	$C_{16}H_{18}N_2O_4$
16	CH_2	C_6H_2-3,4,5-$(OCH_3)_3$	H	122–123	EtOH		$C_{16}H_{20}N_2O_3$
17	CO	$C_6H_4CF_3$-*m*	H	128–132	EtOH	B	$C_{14}H_{11}F_3N_2O$
18	CH_2	$C_6H_4CF_3$-*m*	H	154–170 (0.1 mm)[d]			$C_{14}H_{13}F_3N_2$
19	CO	$C_6H_4OCH_3$-*p*	H	117–118	EtOH–H_2O	B	$C_{14}H_{14}N_2O_4$
20	CH_2	$C_6H_4OCH_3$-*p*	H	76–78	EtOH		$C_{14}H_{16}N_2O$
21	CO	C_6H_3-3,4-$(OCH_3)_2$	H	159–163	EtOH	A	$C_{15}H_{16}N_2O_3$
22	CH_2	C_6H_3-3,4-$(OCH_3)_2$	H	97–98	EtOH		$C_{15}H_{18}N_2O_2$
23	CO	C_6H_5-*p*-$OCH_2C_6H_5$	H	155–163	THF	A	$C_{20}H_{18}N_2O_2$
24	CH_2	C_6H_5-*p*-$OCH_2C_6H_5$	H	142–144	EtOH		$C_{20}H_{20}N_2O$
25	CO	C_6H_3-3,5-$(OCH_3)_2$	H	115–120	EtOH	A	$C_{15}H_{16}N_2O_3$
26	CH_2	C_6H_3-3,5-$(OCH_3)_2$	H	93–95	EtOH		$C_{15}H_{18}N_2O_2$
27	CO		H	Oil[a]		C	
28	CH_2		H	Oil[a]			
29	CO	C_6H_2-3,4,5-$(OCH_3)_3$	6-CH_3	177–187	EtOH	A	$C_{17}H_{20}N_2O_4$
30	CH_2	C_6H_2-3,4,5-$(OCH_3)_3$	6-CH_3	150–153	EtOH		$C_{17}H_{22}N_2O_3$
31	CO		H	157–159	EtOH	C	$C_{15}H_{15}ClN_2O_3$
32	CH_2		H	131–133	EtOH		$C_{15}H_{17}ClN_2O_2$
33	CH_2	C_6H_3-2,4-$(OCH_3)_2$	H	71–74	EtOH[b]	D	$C_{15}H_{18}N_2O_2$

[a] Carried on directly to next step. [b] Required chromatography on silica. [c] Compounds analyzed for C, H, and N; **8, 10,** and **12,** analyzed for N only. [d] Boiling point.

3-substituted quinazolinones were carried out using NaH in DMSO to give the desired products.

The diamines required for the ring-closure step were prepared in several different ways (Chart II). The most convenient method is reduction of the appropriately substituted 2-aminobenzamide with $LiAlH_4$ in dioxane. For reduction of the benzamides in which methoxy groups were present, THF was substituted for dioxane since $LiAlH_4$ reduction in the latter solvent caused extensive decomposition.

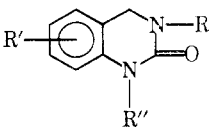
The 2-aminobenzamides were prepared by the reaction of isatoic anhydride or a substituted isatoic anhydride with the appropriate amine. This reaction could be carried out under two different conditions depending upon the availability of the amine: reaction of isatoic anhydride with 3 equiv of the amine in ethanol (method B) or reaction of isatoic anhydride with 1 equiv of the amine in dioxane containing a catalytic amount of NaOH (method A). Aromatic amines which contain two *ortho* substituents or one bulky *ortho* substituent would not react with isatoic anhydride even at elevated temperatures. For the synthesis of these compounds, the amide was prepared from the amine and *o*-nitrobenzoyl chloride followed by catalytic reduction of the nitro group (method C).

An alternative method for the preparation of the diamines with *ortho* substituents on the aromatic R group involved the formation of a Schiff base from *o*-nitrobenzaldehyde and the amine followed by catalytic reduction (method D). However, the latter reaction only proceeded in poor yield.

The 3-dialkylaminoalkylquinazolinones were prepared in a similar manner, starting with the 1-substituted isatoic anhydride (Chart III). N-Phenylisatoic anhydride could be prepared in excellent yield by oxidation of N-phenylisatin with peracetic acid or with *m*-chloroperbenzoic acid.[3] Treatment of this compound with ammonia gave the 2-anilinobenzamide which was reduced ($LiAlH_4$) to the diamine and ring closed as before to give the 1-phenyl-3,4-dihydro-2(1H)-quinazolinone. Alkylation with 2-diethylaminoethyl chloride gave the desired compound. Following a

(3) R. A. Scherrer, U. S. Patent 3,238,201 (1966).

TABLE II



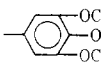
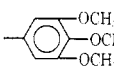
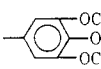
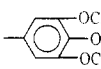
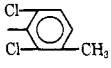
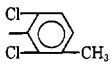
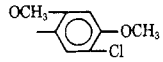
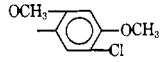
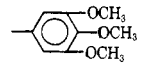
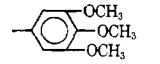
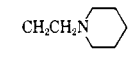
Compd	R	R′	R″	Salt	Mp, °C	Solvent	Method	Formula[a]	Antiinflam act., MED, mg/kg Foot edema[c]	Cotton granuloma[d]
34	C_6H_5	H	H		189–191	EtAc	E	$C_{14}H_{12}N_2O$		
35	C_6H_5	H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	134–136	EtOH		$C_{22}H_{27}N_3O_5$	200	50
36	C_6H_5	H	$CH_2CHN(CH_3)_2$ (CH₃)	$C_2H_2O_4$	203–206	EtOH		$C_{21}H_{25}N_3O_5$	*b*	
37	C_6H_5	H	$CH_2CH_2N[CH(CH_3)_2]_2$	$C_2H_2O_4$	113–116	EtOH		$C_{24}H_{31}N_3O_5$	200	100
38	C_6H_5	H	$CH_2CH_2N(CH_3)CH_2C_6H_5$	$C_2H_2O_4$	162–164	EtOH		$C_{26}H_{27}N_3O_5$	200	100
39	C_6H_5	H	$CH_2CH_2N(CH_3)C(CH_3)_3$		Oil			$C_{21}H_{27}N_3O$	200	100
40	C_6H_5	6-Cl	H		160–165	EtAc	E	$C_{14}H_{11}ClN_2O$		
41	C_6H_5	6-Cl	$CH_2CH_2NEt_2$	$C_2H_2O_4$	171–173	EtOH		$C_{22}H_{26}ClN_3O_5$	200	>100
42	C_6H_4Cl-*p*	H	H		207–209	EtOH	E	$C_{14}H_{11}ClN_2O$		
43	C_6H_4Cl-*p*	H	$CH_2CH_2NEt_2$		Oil			$C_{20}H_{24}ClN_3O$	200	>100
44	C_6H_4Cl-*p*	H	$CH_2CH_2CH_2N$–NC_6H_4Cl-*m*		162–169	EtOH		$C_{27}H_{28}Cl_2N_4O$	*b*	
45	C_6H_4Cl-*p*	H	$CH_2CH_2CH_2N(CH_3)_2$	$C_2H_2O_4$	186–188	EtOH		$C_{21}H_{14}ClN_3O_5$	200	>100
46	C_6H_3-2,4-$(CH_3)_2$	H	H		175–200	EtOH	E	$C_{16}H_{16}N_2O$		
47	C_6H_3-2,4-$(CH_3)_2$	H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	165–166	EtOH		$C_{24}H_{31}N_3O_5$	*b*	100
48		H	H		218–230	EtOH	E	$C_{18}H_{22}N_2O$	200	>100
49		H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	145–147	EtOH		$C_{26}H_{37}N_3O_5$	200	>100
50	$CH_2C_6H_5$	H	H		198–208	EtOH	E	$C_{15}H_{14}N_2O$	200	100
51	$CH_2C_6H_5$	H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	137–140	EtOH		$C_{23}H_{29}N_3O_5$	*b*	
52	$CH_2CH_2CH_3$	H	$CH_2CH_2NEt_2$		Oil			$C_{17}H_{27}N_3O$	200	>100
53	$C_6H_4CF_3$-*m*	H	H		130–133	EtOH	F	$C_{15}H_{11}F_3N_2O$		
54	$C_6H_4CF_3$-*m*	H	$CH_2CH_2NEt_2$		Oil			$C_{21}H_{28}F_3N_3O$	200	100
55		H	H		187–189	THF	F	$C_{17}H_{18}N_2O_4$	>200	10
56		H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	89–97	EtOH		$C_{25}H_{33}N_3O_8$	200	5
57		H	CH_2CH_2N	$C_2H_2O_4$	155–157	EtOH		$C_{26}H_{35}N_3O_9$	*b*	
58		H	CH_2CH_2N–NCH_3	$C_2H_2O_4$	229–234	EtOH		$C_{28}H_{36}N_4O_{12}$	*b*	
59	$C_6H_4OCH_3$-*p*	H	H		243–245	THF	F	$C_{15}H_{14}N_2O_2$		
60	$C_6H_4OCH_3$-*p*	H	$CH_2CH_2NEt_2$		Oil			$C_{21}H_{27}N_3O_2$	200	25
61	C_6H_3-3,4-$(OCH_3)_2$	H	H		180–181	THF	F	$C_{16}H_{16}N_2O_3$		
62	C_6H_3-3,4-$(OCH_3)_2$	H	$CH_2CH_2NEt_2$		Oil			$C_{22}H_{29}N_3O_3$	40	>100
63	C_6H_5-*p*-$OCH_2C_6H_5$	H	H		205–208	THF	F	$C_{21}H_{18}N_2O_2$		
64	C_6H_5-*p*-$OCH_2C_6H_5$	H	$CH_2CH_2NEt_2$		68–69	EtOH		$C_{27}H_{31}N_3O_2$	*b*	
65	C_6H_4OH-*p*	H	H		299–302	DMF–H_2O		$C_{14}H_{12}N_2O_2$		
66	C_6H_4OH-*p*	H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	157–158	EtOH		$C_{22}H_{27}N_3O_6$	200	>100
67	C_6H_3-3,5-$(OCH_3)_2$	H	H		130–134	EtOH	F	$C_{16}H_{16}N_2O_3$		
68	C_6H_3-3,5-$(OCH_3)_2$	H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	134–136	EtOH–Et_2O		$C_{24}H_{31}N_3O_7$		
69	C_6H_3-2,4-$(OCH_3)_2$	H	H		253–256	THF	F	$C_{16}H_{16}N_2O_4$		

TABLE II (*Continued*)

Compd	R	R′	R″	Salt	Mp, °C	Solvent	Method	Formula[a]	Antiinflam. act., MED, mg/kg Foot edema[c]	Cotton granuloma[d]
70	C_6H_3-2,4-$(OCH_3)_2$	H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	203–205	EtOH		$C_{24}H_{31}N_3O_7$	200	>100
71		H	H		221–223	EtOH	F	$C_{15}H_{12}N_2Cl_2O$		
72		H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	156–158	EtOH		$C_{23}H_{27}Cl_2N_3O_5$	200	>100
73		H	H		235–238	THF	F	$C_{16}H_{13}ClO_3N_2$		
74		H	$CH_2CH_2NEt_2$	$C_2H_2O_4$	140–143	EtOH		$C_{24}H_{30}ClN_3O_7$		
75		6-CH_3	H		205–215	THF	F	$C_{18}H_{20}N_2O_4$		
76		6-CH_3	$CH_2CH_2NEt_2$	$C_2H_2O_4 \cdot 0.5H_2O$	136–145	EtOH		$C_{26}H_{35}N_3O_8 \cdot 0.5H_2O$	200	100
77	H	H	C_6H_5		213–214	THF	F	$C_{14}H_{12}N_2O$		
78	$CH_2CH_2NEt_2$	H	C_6H_5	$C_2H_2O_4$	169–170	EtOH		$C_{22}H_{27}N_3O_5$	200	>100
79	H	H	CH_3		143–144	EtOH	F	$C_9H_{10}N_2O$	200	20
80	$CH_2CH_2NEt_2$	H	CH_3	$C_2H_2O_4$	133–134	EtOH		$C_{17}H_{25}N_3O_5$	40	>100
81		H	CH_3	$C_2H_2O_4$	167–168	EtOH		$C_{18}H_{25}N_3O_5$	200	>100
82	$CH_2CHN(C_2H_5)_2$ (CH₃ branch)	H	CH_3		Oil			$C_{16}H_{25}N_3O$	200	>100
83	H	H	$C_6H_5CH_2$		140–155	EtOH	F	$C_{15}H_{14}N_2O$		
84	$CH_2CH_2NEt_2$	H	$C_6H_5CH_2$	$C_2H_2O_4$	153–155	EtOH		$C_{23}H_{29}N_3O_5$	200	>100

[a] All compounds analyzed for C, H, and N. [b] Insufficient data to state potency. [c] Subcutaneously. [d] Intragastrically.

similar sequence, N-methylisatoic anhydride was converted to 1-methyl-3-(2-diethylaminoethyl)-3,4-dihydro-2(1H)-quinazolinone. The diamine required for preparation of the 1-benzyl derivative was synthesized by $LiAlH_4$ reduction of 2-benzalaminobenzamide (Chart III).

Biological Activity.—This series of compounds was tested in two standard assays for antiinflammatory activity. The inhibition of the local edema in the rat paw induced by carrageenin was measured both subcutaneously and intragastrically.[4] Compounds active in this test were further tested intragastrically against the cotton pellet induced granuloma growth in the rat.[5] If a compound was sufficiently active in these tests, it was tested as an inhibitor of the adjuvant-induced arthritis in rats.[6]

Phenylbutazone was used as a standard for comparison and was active in the assays as follows: foot edema, 40 mg/kg, cotton pellet granuloma, 25 mg/kg, and adjuvant arthritis, 25 mg/kg. In Table II are reported the results of the biological testing. Compounds active at 200 mg/kg subcutaneously in the foot edema test were tested at 25 mg/kg orally. Since we were not interested in compounds less active than 25 mg/kg orally, minimum effective doses of 25–200 mg/kg were not determined. Compounds active at 100 mg/kg orally in the cotton pellet granuloma test were tested at 25 mg/kg orally with no intermediate dosages used. Of the compounds tested, only **55**, **56**, **60**, **79**, and **80** were equal to or better than phenylbutazone in one of the assays. The most interesting compound is **56** which is five times as active as phenylbutazone in the granuloma test. However, this compound is only one-fifth as active as phenylbutazone in the foot edema assay. Follow-up testing in the polyarthritic rat showed that **56** is inactive at 25 mg/kg.

(4) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).
(5) P. Meier W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).
(6) B. B. Newbould, *Brit. J. Pharmacol.* **21**, 127 (1967).

Experimental Section

2-Amino-N-substituted Benzamides (Table I). Method A.—To a stirred suspension of 0.4 mole of isatoic anhydride in 600 ml of dioxane was added 1.5 g of powdered NaOH and 0.4 mole of the appropriate amine. The suspension was heated slowly to reflux (1 hr) during which evolution of CO_2 occurred and a clear solution resulted. After 2 hr of reflux, the solution was cooled and filtered. The dioxane was removed *in vacuo* and the residue was recrystallized from the appropriate solvent.

Method B.—To a stirred suspension of 0.4 mole of isatoic anhydride in 200 ml of anhydrous EtOH was added 1 mole of the appropriate amine slowly to control the evolution of CO_2. After reaction had subsided the solution was heated on a steam bath for 0.5 hr and poured into H_2O. Filtration of the solid and recrystallization from the appropriate solvent gave the desired compound.

Chart II

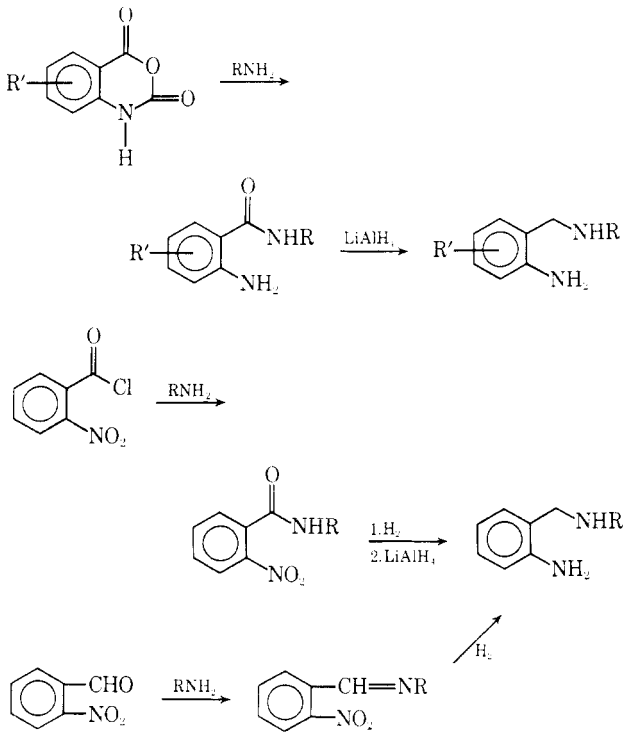
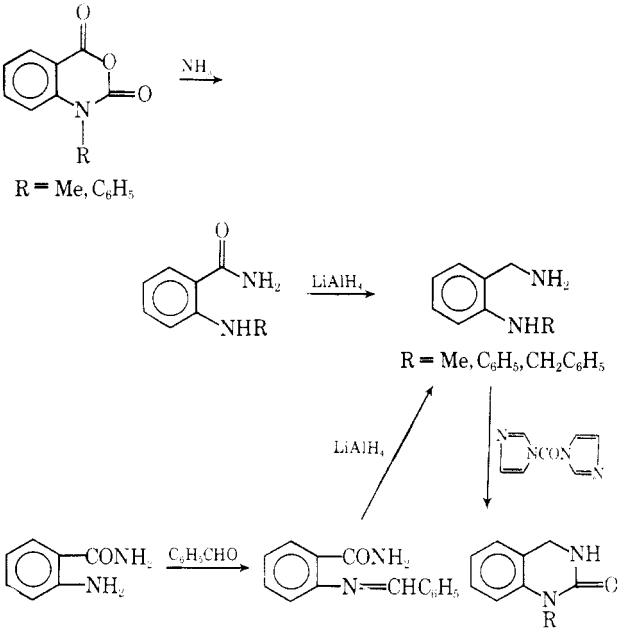


Chart III



Method C.—To a stirred refluxing solution of 0.114 mole of the amine in C_6H_6 (250 ml) containing 0.114 mole of anhydrous K_2CO_3 was added a solution of 0.114 mole of 2-nitrobenzoyl chloride in C_6H_6 (20 ml) over a period of 0.5 hr. After addition, the suspension was refluxed for 2.5 hr and cooled, and 200 ml of H_2O was added. The organic layer was separated, washed (H_2O), dried, and evaporated to give the desired N-substituted 2-nitrobenzamide. A solution of the nitro compound (0.044 mole) in 1 l. of THF was hydrogenated at atmospheric pressure and room temperature using 10 g of Raney Ni as catalyst to give the desired 2-amino-N-substituted benzamide.

Method D. 2-Amino-N-(2,4-dimethoxyphenyl)benzylamine (33).—A solution of 25.0 g of 2-nitrobenzaldehyde and 25.0 g of 2,4-dimethoxyaniline in 300 ml of C_6H_6 was refluxed 4 hr with continuous removal of H_2O. The solution was cooled and charcoaled, and the product crystallized by addition of petroleum ether (bp 60–90°) giving 39.1 g of N-(2-nitrobenzal)-2,4-dimethoxyaniline, mp 79–81°. This product was hydrogenated in 1 l. of MeOH at atmospheric pressure and room temperature using 15 g of Raney Ni as catalyst until 1 mole of H_2 was added. The oil obtained on filtration and evaporation of the MeOH was dissolved in 125 ml of THF and refluxed for 18 hr under N_2 with 10 g of $LiAlH_4$. The resulting suspension was decomposed by successive addition of 10 ml of H_2O, 10 ml of 15% aqueous NaOH, and 30 ml of H_2O. Filtration and evaporation of the solvent gave a dark oil. Chromatography on silica using 10% EtOAc–PhH as eluent gave 3.9 g of white crystals, mp 71–74°.

1- or 3-Substituted 3,4-Dihydro-2(1H)-quinazolinones (Table II). Method E.—To a stirred solution of the appropriate diamine (0.15 mole) in 1 l. of toluene at 10° was added a solution of 0.2 mole of $COCl_2$ in 200 ml of toluene, over a period of 1 hr. The resulting suspension was refluxed for 1 hr to give a clear solution. The solvent was evaporated and the solid was recrystallized to give the desired product.

Method F.—To a stirred solution of 0.04 mole of the diamine in 50 ml of THF was added 0.05 mole of 1,1′-carbonyldiimidazole and the solution stirred at room temperature for 3 hr. After 18 hr of reflux the solution was cooled. In many cases the product crystallized directly on cooling. If no crystals were obtained, the reaction mixture was poured into H_2O and the solid was filtered and recrystallized.

Alkylation of 3-Substituted 3,4-Dihydro-2(1H)-quinazolinones. To a stirred solution of 0.04 mole of the 3-substituted 3,4-dihydro-2(1H)-quinazolinone in 50 ml of DMSO under N_2 was added 0.04 mole of NaH. After 0.5 hr the alkyl halide (0.05 mole) was added and the reaction stirred at room temperature 18 hr. The mixture was poured into H_2O and extracted (Et_2O), and the ether extracts were dried (K_2CO_3). Evaporation of Et_2O gave the crude product. In most cases the oxalate was prepared by addition of an excess of a solution of oxalic acid in EtOH to a concentrated solution of the amine in EtOH. When the oxalates could not be crystallized, the free amine was formed by washing a solution of the crude oxalate with Et_2O, making basic with NH_4OH, and extracting the product (Et_2O).

2-Amino-N-substituted Benzylamines (Table I).—To a hot, stirred suspension of 15.0 g of $LiAlH_4$ in 200 ml of dioxane, under N_2, was added a solution of the 2-amino-N-substituted benzamide (0.125 mole) in 200 ml of dioxane. The resulting suspension was refluxed for 18 hr and decomposed by successive addition of 15 ml of H_2O in 15 ml of dioxane, 15 ml of 15% aqueous NaOH, and 45 ml of H_2O. Filtration and evaporation of the dioxane gave the diamine which was recrystallized from the appropriate solvent.

For compounds **16**, **22**, **24**, **30**, and **32**, THF was used as the solvent, since the reductions in dioxane produced the desired products only in low yields.

3-(*p*-Hydroxyphenyl)-3,4-dihydro-2(1H)-quinazolinone (65).—A solution of 5 g of 3-(*p*-benzyloxyphenyl)-3,4-dihydro-2(1H)-quinazolinone in 50 ml of DMF was hydrogenated at atmospheric pressure and room temperature using 0.2 g of 5% Pd–C as catalyst. The filtered solution was diluted (H_2O) to give 1.2 g of silvery crystals, mp 299–302°.

1-(2-Diethylaminoethyl)-3-(*p*-hydroxyphenyl)-3,4-dihydro-2(1H)-quinazolinone oxalate (66).—A solution of 5.0 g of 1-(2-diethylaminoethyl)-3-(*p*-benzyloxyphenyl)-3,4-dihydro-2(1H)-quinazolinone in 200 ml of EtOH was hydrogenated at atmospheric pressure and room temperature using 0.5 g of 5% Pd–C as catalyst. Filtration and evaporation of the solvent gave an oil which was dissolved in EtOH and treated with excess oxalic acid in EtOH. The crystals formed were recrystallized from EtOH to give 3.0 g of white crystals, mp 157–158°.

5-Methylisatoic Anhydride.—To a solution of 50 g of 5-methylisatin in 900 ml of AcOH was added 200 ml of 40% AcO_2H. After stirring for 3 days the solution was poured into H_2O, and the solid was filtered and washed (H_2O) to give 36.5 g of light orange crystals, mp 215–250°.

2-Benzylaminobenzylamine.—To a stirred hot suspension of 20 g of $LiAlH_4$ in 200 ml of dioxane was added slowly a suspension of 2-benzalaminobenzamide (36 g) in 300 ml of dioxane. The suspension was stirred and refluxed for 18 hr and then decomposed by successive addition of 20 ml of H_2O in 20 ml of dioxane, 20 ml of 15% aqueous NaOH solution, and 60 ml of H_2O. The reaction mixture was filtered, the dioxane was evaporated *in vacuo*, and the oil was distilled to give 18.8 g of a colorless oil, bp 140–144° (0.15 mm). *Anal.* ($C_{14}H_{16}N_2$) C, H, N.

2-Benzalaminobenzamide.—A solution of 27.2 g (0.2 mole) of anthranilamide and 21.2 g (0.2 mole) of benzaldehyde in 300 ml of C_6H_6 was refluxed 2.5 hr with continuous removal of

H_2O. On cooling, a solid appeared which was filtered to give 36 g of amber crystals, mp 150–153°. *Anal.* ($C_{14}H_{12}N_2O$) C, H, N.

2-Aminomethyldiphenylamine.—To a hot stirred suspension of 15 g of $LiAlH_4$ in 200 ml of dioxane under N_2 was added 31 g of N-phenylanthranilamide in 200 ml of dioxane. After addition, the suspension was stirred and refluxed for 18 hr. Decomposition by successive addition of 15 ml of H_2O, 15 ml of 15% aqueous NaOH, and 45 ml of H_2O, filtration, and evaporation of the dioxane gave a colorless oil, bp 140–160° (0.1 mm) (20.1 g). This compound was used without further purification in the next step.

N-Phenylanthranilamide.—To a stirred suspension of 36.8 g of N-phenylisatoic anhydride in 200 ml of EtOH was added 50 ml of 28% aqueous NH_3 dropwise. After addition, the solution was refluxed for 0.5 hr and cooled. Addition of H_2O gave 31.0 g of white crystals. Recrystallization from EtOH–H_2O gave crystals, mp 117–123°. *Anal.* ($C_{13}H_{12}N_2O$) C, H, N.

N-Phenylisatoic Anhydride.—To a solution of 25.0 g of N-phenylisatin in 600 ml of AcOH was added 150 ml of 40% AcO_2H. After stirring for 3 days at room temperature the solution was poured into H_2O and filtered, and the solid was recrystallized (C_6H_6) to give 14.9 g of light amber crystals, mp 174–177°. *Anal.* ($C_{14}H_{19}NO_3$) C, H, N.

2-Methylaminobenzamide.—To a stirred suspension of 50 g of N-methylisatoic anhydride in 200 ml of EtOH was added dropwise 50 ml of 28% aqueous NH_3. After addition, the solution was heated on a steam bath for 2 hr. On cooling, a solid formed to give 31 g of colorless crystals, mp 158–161°. This compound was used without further purification in the next step.

2-Methylaminobenzylamine.—To a hot stirred suspension of 15 g of $LiAlH_4$ in 200 ml of dioxane was added dropwise a hot solution of 31 g of 2-methylaminobenzamide in 300 ml of dioxane. The reaction was refluxed for 18 hr and decomposed by successive addition of 15 ml of H_2O in 15 ml of dioxane, 15 ml of 15% aqueous NaOH solution, and 45 ml of H_2O. Filtration and evaporation of the solvent gave a colorless oil, bp 88–96° (0.15 mm) (22.6 g). *Anal.* ($C_{18}H_{12}N_2$) C, H, N.

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Notes

Synthesis of Potential Antimalarial Agents. I.[1] 6- and 6,9-Disubstituted Purines

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The mode of action of chloroquine and related antimalarial compounds is thought to be primarily the inhibition of the enzymatic synthesis of DNA.[2] The activity of chloroquine in the mouse is attributed to the 25-fold greater accumulation of the drug in parasitized (*Plasmodium berghei*) than in nonparasitized erythrocytes.[2] A number of antimetabolites such as purine-6(1H)-thione are also known to interfere with nucleic acid biosynthesis,[3] but apparently have no antimalarial activity.[4] Although the association of purine-6(1H)-thione with rat RNA might be one mode by which this compound interferes with cellular metabolism,[5] the lack of antimalarial activity of this and related compounds might be due to the lack of selective uptake or binding with parasitized erythrocytes. Derivatives of the cytotoxic purines that might concentrate selectively in parasitized erythrocytes were prepared by the attachment of well-known antimalarial side changes.

This study included the preparation of both 6-substituted and 6,9-disubstituted purines, the yields and properties of which are listed in Table I. Reaction of a 6-chloropurine with amines containing antimalarial side chains gave the 6-N-substituted adenines **1–10**, **18–25**, **33–36**, and **44**. The reaction conditions are given in Table I, and typical procedures are given in the Experimental Section.[6–10] The 6-chloropurines containing an antimalarial side chain in the 9 position of the ring were prepared in two steps from 5-amino-4,6-dichloropyrimidine.[11,12] Standard procedures were used to convert these 6-chloropurines to the 9-substituted purine analogs listed in Table I.

The 49 compounds prepared in this study, 7- and 9-benzyl-6-(*p*-chloroanilino)-9H-purine, ethyl 9-(6-*p*-chloroanilino)-9H-purineacetate, and 6-methylthio-9-β-D-ribofuranosyl-9H-purine were submitted for evaluation against mice infected with a lethal dose of *P. berghei*.[13] Although screening results are incomplete, no significant activity has yet been observed.

(1) This work was carried out for the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, under Contract No. DA-49-193-MD-2999. This is Contribution No. 409 from the Army Research Program on Malaria.

(2) (a) F. E. Hahn, R. L. O'Brien, J. Ciak, J. L. Allison, and J. G. Olenick, *Military Med.*, **131** (Suppl), 1071 (1966); (b) P. B. Macomber, R. L. O'Brien, and F. E. Hahn, *Science*, **152**, 1374 (1966).

(3) For a review of this subject, see J. A. Montgomery, *Progr. Drug Res.*, **8**, 433 (1965).

(4) No reference was found in the literature to antimalarial activity of these compounds, and the conclusion that they possess no antimalarial activity was confirmed by Dr. T. R. Sweeney.

(5) H. J. Hansen and S. B. Nadler, *Proc. Soc. Exp. Biol. Med.*, **107**, 324 (1961).

(6) For the preparation of *p*-(2-aminoethyl)benzenesulfonamide, see E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Amer. Chem. Soc.*, **62**, 2099 (1940).

(7) We wish to thank Eastman Chemical Products, Inc., for a sample of 5-amino-2,2-dimethylpentanol.

(8) For the preparation of 4-amino-α-diethylamino-*o*-cresol, see J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Amer. Chem. Soc.*, **70**, 1363 (1948).

(9) Acid hydrolysis of 4-acetamido-2,6-bis(1-pyrrolidinylmethyl)phenol gave 4-amino-2,6-bis(1-pyrrolidinylmethyl)phenol; see ref 8.

(10) For the preparation of *p*-amino-N,N′-bis(2-methoxyethyl)benzamidine, see H. V. Peckmann, *Ber.*, **30**, 1779 (1897).

(11) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Pharm. Chem.*, **5**, 866 (1962).

(12) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **80**, 409 (1958).

(13) For a description of the test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).